TABLE 3.—*Maternal smoking and prematurity*

(Figures in parentheses are the absolute number of premature births)

Author, reference	Premature by: Weight	Premature by: Duration of gestation		Percent of premature infants: Nonsmokers		Percent of premature infants: Smokers		Mean duration of pregnancy: Nonsmokers	Mean duration of pregnancy: Smokers	Comments
Yerushalmy (*54*).	<5½ lbs.			5.9	(36)	8.1	(30)			
Murdoch (*30*).	<2,500 g.			3.3	(8)	13.6	(35)			
O'Lane (*33*).	<2,500 g.			5.1	(29)	11.8	(55)			
Zabriskie (*58*).	<2,500 g.			3.83	(40)	9.93	(95)			Cigarettes per day: *Prematurity* <10 ..... 6.54 (260) 10–20 ..... 9.11 (395) 20–30 .....14.39 (264) >30 .....10.53 (38)
Yerushalmy (*54*).	<5 lbs. 8 oz.		White	3.5	(112)	6.4	(138) ($p<0.01$)			Infants of smoking mothers weighed less than infants of nonsmoking mothers in each gestational age.
			Negro	4.9	(46)	13.4	(64)			
		<37 weeks	White	†5.9	(188)	6.5	(140)			† Difference between smokers and nonsmokers not significant.
			Negro	13.4	(125)	16.7	(80)			
McDonald and Lanford (*26*).	<2,500 g.			*Cigarettes per day*						
				4.6	(4)	<10	4.8	(2)		
						>10	8.3	(4)		
Peterson et al., (*34*).	<2,500 g.			*Cigarettes per day*						Overall incidence of prematurity in smokers vs. nonsmokers significant at $p<0.001$.
				2.5	(111)	1–10	3.0	(35)		
						11–20	4.8	(80)		
						>20	3.4	(16)		

TABLE 3.—*Maternal smoking and prematurity (cont.)*

(Figures in parentheses are the absolute number of premature births)

Author, reference	Premature by		Percent of premature infants				Mean duration of pregnancy		Comments
	Weight	Duration of gestation		Nonsmokers	Smokers		Nonsmokers	Smokers	
Peterson et al., (contd.) (34).		<37 weeks		*Cigarettes per day*					
				1.3 (58)	1–10	1.4 (16)			
					11–20	2.3 (38)			
					>20	2.4 (11)			
Robinson (37).	<2,500 g.			16.5 (152)		31.0 (181)			
Underwood et al., (50).	<2,500 g.		Group:		*Cigarettes per day*				Percentages and absolute number of premature births are based on 16,158 pregnancies recorded in 4,440 women. Group I. Smokers vs. nonsmokers $p<0.025$. Group II., III. Smokers vs. nonsmokers $p<0.001$.
			I		4.5 (108)	<10 4.2			
						10–20 5.9			
						<20 7.2			
			II		7.5 (42)	<10 12.6			
						10–20 12.3			
						>20 15.9			
			III		9.9 (770)	<10 14.1			
						10–20 14.8			
						>20 10.2			
Downing and Chapman (7).	No data	No data		2.2 (66)		3.3 (88)			
Reinke and Henderson (36).	<2,500 g.			10.6 (163)		16.7 (270)	37.7 weeks	37.67 weeks	$p<0.001$
		<35 weeks		20.3 (313)		22.8 (368)			$p>0.05$

TABLE 3.—*Maternal smoking and prematurity (cont.)*

(Figures in parentheses are the absolute number of premature births)

Author, reference	Premature by		Percent of premature infants			Mean duration of pregnancy		Comments
	Weight	Duration of gestation	Nonsmokers	Smokers		Nonsmokers	Smokers	
Underwood et al., (51).	<2,500 g.		*Cigarettes per day*					Prematurity by birth weight rose directly to a significant degree ($p<0.01$) with each smoking category.
			5.7 (1,417)	1–10	7.5 (571)			
				11–30	9.4 (1,358)			
				>30	11.2 (176)			
		<36 weeks	5.8 (1,442)	1–10	6.9 (525)			Data suggested that smoking in any trimester decreased birth weight.
				11–30	7.5 (1,084)			
				>30	7.5 (118)			
Buncher (4).						*Births*		† Smokes 20 cigarettes per day.
						Male 39.55 weeks	† 39.35 weeks	
						Female 39.69 weeks	† 39.51 weeks	
Butler and Alberman (5).	<2,500 g.		5.4 (602)		9.3 (433)			
Terris and Gold (47).								A significant ($p<0.01$) difference was found between percent of mothers who smoked and those who had premature deliveries and the control group.

mortality rate was found for both stillbirths and neonatal deaths, and was somewhat greater for stillbirths but not significantly so (see Butler, table 4). The authors state that "... the differences between mortality rates in babies of smokers and nonsmokers practically disappear when they are compared within groups of similar birthweights ... It therefore seems reasonable to conclude that the increased mortality found in babies of mothers who smoke is accounted for by the overall excess of low birthweight babies in this group ..." with their attendant high risks.

In 1964, Yerushalmy (*54*) reported on a group of 6,800 women whose pregnancies terminated in single, live births, excluding stillbirths and abortions. The study was prospective and was controlled for maternal age and parity. He noted that neonatal mortality in infants born to smoking mothers and weighing less than 2,500 grams was significantly less than that of small infants born to nonsmoking mothers. He referred to these small infants of smoking mothers as being "apparently healthier" than those infants weighing less than 2,500 grams who were born to nonsmoking mothers.

As this report showed, when compared to infants weighing more than 2,500 grams, a small (<2,500 grams) infant faces a greatly increased risk of neonatal mortality, whether it is born to a smoking mother or to a nonsmoking mother (*54*). The neonatal death rate for the small infants of smoking mothers was less than that for small infants of nonsmoking mothers, but neither group can be considered "healthy," having sharply elevated death rates. The overall neonatal mortality for babies born to white smoking mothers was 12 percent higher than that for babies born to nonsmoking mothers. This is not significantly greater than the neonatal mortality of infants born to nonsmoking mothers. On the other hand it is also not significantly different from the 31 percent excess mortality reported by Butler, et al. (*5*), which is statistically significant.

Interpretation of the neonatal mortality among the infants weighing less than 2,500 grams in the Yerushalmy study is difficult. By considering only live births, the series may have included a higher proportion of infants whose smaller birthweight was primarily due to a modest growth retarding influence of maternal smoking and not to other more serious congenital defects and intrauterine influences. Butler, et al. (*5*) have shown that smoking mothers have significantly more stillbirths than nonsmoking mothers, and Russell, et al. (*39*) have found this to be true for both stillbirths and abortions.

For reasons which aren't clear, smoking mothers have been found to have a reduced incidence of preeclamptic toxemia as compared to nonsmoking mothers (*51*). However, given the presence of

TABLE 4.—*Comparison of abortion, stillbirth, and neonatal death in smoking and nonsmoking mothers*

NS = Nonsmokers SM = Smokers

Author, reference	Numbers								Rates/1,000 total births						Comments
	Total births		Abortions		Stillbirths		Neonatal deaths		Abortions		Stillbirths		Neonatal deaths		
	NS	SM	NS	SM	NS	SM	NS	SM	NS	SM	NS	SM	NS	SM	
Lowe (*28*).	1,155	668			†47						†23.0	†30.0			† Includes first-day deaths.
Frazier et al., (*12*).	1,717	1,019			†11	†16	40	28			†6.4	†15.5	23.3	27.5	† "Fetal death".
Savel and Roth (*41*).	White														
	383	428			2	3	4	2			5.2	7.0	10.4	4.7	
	Negro														
	364	240			8	4	5	3			22.0	16.7	13.7	12.5	
O'Lane (*33*).	1,027	887	91	112					88.6	126.3					
Zabriskie (*58*).	2,850	2,769	250	348					87.7	125.7					
Yerushalmy (*54*).	White														
	3,218	2,163					40	30					12.4	13.9	
	Negro														
	939	480					22	11					23.4	22.9	
Peterson et al., (*34*).	4,455	3,285									0.6	1.2	4.0	0.9	

TABLE 4.—*Comparison of abortion, stillbirth, and neonatal death in smoking and nonsmoking mothers (cont.)*

NS = Nonsmokers SM = Smokers

Author, reference	Numbers								Rates/1,000 total births						Comments
	Total births		Abortions		Stillbirths		Neonatal deaths		Abortions		Stillbirths		Neonatal deaths		
	NS	SM	NS	SM	NS	SM	NS	SM	NS	SM	NS	SM	NS	SM	
Downing and Chapman (7).	3,029	2,630	126	107	†32	†29			41.6	40.7	†10.6	†11.0			† Stillbirth plus neonatal death.
Underwood et al., (51).	24,896	28,629									8.4	8.7	†11.3	†12.1	† Excludes perinatal deaths in premature infants ($p>0.05$).
Russell et al., (39).	‡BP:														† Includes abortion, stillbirth, and neonatal death.
	<140/90	984 496			†27	†32					†27	†65			‡ Blood pressure.
	=140/90	340 117			†14	†8					41	68			
	>140/90	138 35			†20	†11					145	314			
Tokutata (49).	White														Data based on use of cigarettes only.
	2,555	743			†246	†112					†96	†151			† Includes stillbirths and miscarriages.
	Nonwhite														
	1,235	350			†174	†64					†141	†183			
Butler and Alberman (5).	11,145	4,660			215	129	146	80			19.3	27.6	13.1	17.2	

Source: Modified and expanded from Butler and Alberman (5).

preeclampsia, smoking appears to increase the risk to the fetus because of low birthweight and increased perinatal mortality (*8*).

In a case-control study of sudden, unexpected death in infancy, Steele, et al. (*46*) observed that the percentage of smokers among mothers of cases of sudden, unexpected death, 61.2 percent, was significantly greater than the percentage among mothers of controls, 39.5 percent.

The possible teratogenic effect of maternal smoking has not been adequately evaluated. Although it does not appear to be a major factor, there have been too few studies to determine whether maternal smoking is a significant teratogenic risk (*5, 23, 28, 50*).

Concern has been expressed about the possible long-term effects on the children of women who smoke during pregnancy. Butler (*6*) recently reported the results of a follow-up at age seven of the babies studied in the British Perinatal study of 1958. He found that the children of the mothers who were "heavy" smokers during pregnancy showed significantly decreased height, retardation of reading ability, and lower ratings on "social adjustment" than the children of nonsmoking mothers. The differences were independent of such factors as social class, age of mother, and parity.

EXPERIMENTAL STUDIES

In the past decade, research on the effect of smoking on pregnancy has increased. Summaries of human and animal experimental data in this area of study are found in tables 5 and 6. Elevated carbon monoxide levels have been found in maternal and fetal blood in women who smoke. Carbon monoxide is an inhibitor of carbonic anhydrase and as might be expected the activity of this enzyme is decreased in the cord blood of infants whose mothers smoke. The significance of elevated fetal carbon monoxide is not clear; however, in an extensive monograph on this subject, Longo, (*22*) has concluded that "... the decreased availability of oxygen resulting from elevated (fetal) carboxyhemoglobin levels is probably injurious to fetal tissues." Other changes noted in the infants of smoking mothers have included a mild metabolic acidosis and a higher mean hematocrit (*56*). Two studies (*9, 52*) have shown that placentas of women who smoke have a significantly greater ability to hydroxylate benzo[a]pyrene than the placentas from nonsmokers. Such findings suggest the possibility of fetal exposure to carcinogens; however, the significance of these findings is presently speculative.

Early animal studies (*10, 42*) showed that rats and rabbits exposed to nicotine or cigarette smoke have smaller offspring and more unsuccessful pregnancies than control animals. Recent radio-

TABLE 5.—*Human experimental data on smoking and pregnancy*

Author, year, country, reference	Design of study	Results	Comments
Sontag and Wallace, 1935, U.S.A. (*45*).	Fetal heart rate before and after smoking was studied 81 times in 5 patients.	Average fetal heart rate before smoking was 144.0. The average fetal heart rate for the eighth to the twelfth minute after starting to smoke was 149.0.	
Haddon et al., 1961, U.S.A. (*14*).	Carbon monoxide levels were measured in 50 smokers and nonsmokers in a prenatal clinic. Twenty-six paired maternal and umbilical vein blood specimens were obtained at parturition and tested for CO levels.	(*a*) Carbon monoxide levels were significantly ($p \leq 0.01$) higher in smokers than in nonsmokers. (*b*) Carbon monoxide concentrations in paired cord and maternal blood specimens were approximately equal. (*c*) O_2 carrying capacity in cord and maternal blood was reduced in smokers compared to nonsmokers.	
Heron, 1962, New Zealand (*15*).	58 pregnant smoking women were studied during labor to determine the effect which smoking might have on the "grading" of the infant at birth. CO levels were measured in both mother and fetus.	(*a*) CO levels in maternal and fetal blood were higher in patients who smoked. (*b*) Respirations in infants of mothers who smoked took longer to be established and peripheral cyanosis was more common.	A control group who had never smoked was compared with the survey group.
Kumar and Zourlas, 1963, U.S.A. (*20*).	The *in vivo* effects of cigarette smoking on uterine activity were studied in 17 pregnant gravidas near term and not in labor. The *in vitro* effect of nicotine on human pregnant and nonpregnant myometrial strips was studied.	(*a*) In more than half (10/17), a definite increment in uterine activity was noticed during cigarette smoking. (*b*) No oxytocic effect of nicotine on myometrial strips was noted.	
Young and Pugh 1963, England (*55*).	Blood CO levels were studied in 19 full-term parturient women, 16 of whom had normal deliveries. Six of these smoked 10 to 20 cigarettes a day. Maternal blood was analyzed 15 to 30 minutes prior to delivery. Fetal blood was taken from the placental end of the umbilical vein.	CO content of umbilical vein blood at normal deliveries was .52 and .36 volumes percent in infants of mothers who smoked and mothers who did not smoke, as compared with .33 and .28 volumes percent, respectively, in the maternal venous blood.	Blood CO levels were also studied in nonsmoking male laboratory workers in London and in males in Antarctica.

TABLE 5.—*Human experimental data on smoking and pregnancy (cont.)*

Author, year, country, reference	Design of study	Results	Comments
Mantell, 1964, New Zealand (*25*).	Cord bloods from 50 smokers and 50 nonsmokers were analyzed for carbonic anhydrase activity.	A decrease in carbonic anhydrase activity in the cord bloods of infants whose mothers smoked was noted.	Carbon monoxide is an inhibitor of carbonic anhydrase.
Scoppetta, 1968, Italy (*43*).	CO concentrations were measured in the venous blood of 46 pregnant women, including smokers and nonsmokers. Funicular venous blood was analyzed at the time of delivery.	CO levels were higher in smokers than in nonsmokers. CO concentrations were approximately the same in maternal and funicular venous blood.	
Younoszai et al., 1968, Canada (*56*).	32 women with normal pregnancies were studied of whom 16 smoked >20 cigarettes a day. Both groups of women had normal deliveries and healthy infants. Biochemical changes in the first 48 hours of life were studied in the infants.	(*a*) Mean CO saturation of Hb in the venous blood of the cigarette smoking mothers at the time of delivery was 8.3 percent and in the nonsmoking mothers 1.2 percent. The corresponding mean umbilical vein blood levels were 7.3 percent and .7 percent. (*b*) The blood Ph, pCO_2, and bicarbonate and lactate values in both groups of infants were within normal limits. (*c*) The infants of smoking mothers showed a higher mean hematocrit and mild metabolic acidosis.	
Engel et al., 1969, U.S.A. (*9*).	37 experiments were performed on placental blood samples obtained from 15 pregnancies to determine relative affinity of human fetal Hb for CO and O_2.	Human placental blood has a lower relative affinity for CO than adult blood. It was calculated that the affinity constant of fetal Hb was approximately 20 percent less than that of Hb A.	

TABLE 5.—*Human experimental data on smoking and pregnancy (cont.)*

Author, year, country, reference	Design of study	Results	Comments
Nebert et al., 1969, U.S.A. (*31*).	Aryl hydrocarbon hydroxylase activity was determined in the placentas obtained from 97 women at the time of childbirth; 46 of the women smoked between 20 and 40 cigarettes per day during pregnancy and 51 women were nonsmokers.	Significantly higher ($p<0.001$) levels of aryl hydrocarbon hydroxylase were found in women with a history of cigarette smoking.	
Welch et al., 1969, U.S.A. (*52*).	Benzpyrene hydroxylase and aminoazo dye: N-demethylase activity was measured in 17 human placentas obtained after childbirth from smokers and in 17 human placentas obtained from nonsmokers.	Enzymes were found in the placentas from all 17 smokers. No detectable activity was observed in the placentas of nonsmokers.	

TABLE 6.—*Animal experimental data on the effect of smoking and nicotine on pregnancy*

Author, year, country, reference	Animal	Design of study	Results	Comments
Essenberg et al., 1940, U.S.A. (*10*).	Albino rat.	393 "young" from pregnant rats exposed to tobacco smoke and 113 young from pregnant rats which received parenteral nicotine were studied.	The young of treated mothers were underweight; the young from nicotine injected mothers were more underweight than those from smoked mothers. Increased fetal wastage and neonatal deaths were observed in treated animals as compared to controls.	113 "young" served as controls.
Schoeneck, 1941, U.S.A. (*42*).	Rabbit.	Smoke from one cigarette was blown into the nostril of healthy does by means of a catheter each day. The does were "smoked" daily throughout pregnancy and lactation. 170 young from 28 litters of 7 "smoked" does were studied. The offspring were not subjected to smoking at any time.	(*a*) Offspring from "smoked" female rabbits were smaller at birth than controls (17 percent). (*b*) The stillbirth rate was 10 times as great in the "smoked" group. (*c*) The mortality rate was greater in the offspring of the "smoked" does.	Litters from the previous generation served as controls.
Nishimura and Nakai, 1958, Japan (*32*).	Mouse.	230 pregnant mice were injected, parenterally, with nicotine. Animals were sacrificed at term and mid-pregnancy to investigate the state of the pregnancy and the development of the offspring.	Nicotine had a lethal effect upon mice embryos and also had a teratogenic effect on their skeletal systems.	225 full-term fetuses removed from 29 untreated mice were used as controls.
Gatling, 1964, U.S.A. (*13*).	Chick embryo.	Chicken embryos were treated with doses of nicotine varying from 12 μg. to 1,000 μg. The effects of phenothiazines, corticosteroids, and catecholamines were also studied.	Nicotine induced cephalic hematoma formation and central nervous system depression.	

TABLE 6.—*Animal experimental data on the effect of smoking and nicotine on pregnancy (cont.)*

Author, year, country, reference	Animal	Design of study	Results	Comments
Becker and King, 1966, U.S.A. (*2*).	Rat.	100 primipara pregnant rats received a single heavy subcutaneous injection of nicotine on the 21st day of pregnancy, one day prior to expected term delivery. Fetal wastage, weight of newborns, neonatal deaths, and pregnant animals' responses were noted.	(*a*) Mortality was greater among pregnant rats than among controls. (*b*) Pregnant rats showed more marked hyperventilation and less body temperature depression than controls. (*c*) Delivery was delayed 2 to 4 days. (*d*) The young weighed less than normal and survived "poorly" during the first 48 hours of life	100 nonpregnant rats served as controls.
King and Becker, 1966, U.S.A. (*17*).	Rat.	Pregnant and nonpregnant rats were injected subcutaneously with heavy doses of a 2 percent solution of pure nicotine for the purpose of determining the LD_{50} for females of this strain (Osborne-Mendel). The LD_{50} for neonates of this strain was also determined within 6 to 24 hours of normal birth.	Osborne-Mendel rats LD_{50}: *mg./kg.* Pregnant adults ..... 27.4 Nonpregnant females ..... 33.5 Neonates ..... 14.55 Pregnant rats tended to die significantly later than nonpregnant rats, but their tolerance for nicotine was less.	
Mosier and Armstrong, 1967, U.S.A. (*27*).	Rat.	Alternate pregnant rats received oral nicotine in the dosage of either .05 mg./g. or .10 mg./g. of food. On the 20th day, the rats were killed and the fetuses were removed.	(*a*) On higher nicotine intake, there was lowering of food intake. (*b*) There was no change in fetal weight or length on either concentration. (*c*) There appeared to be no effect on the number of live and "absorbing" fetuses.	

TABLE 6.—*Animal experimental data on the effect of smoking and nicotine on pregnancy (cont.)*

Author, year, country, reference	Animal	Design of study	Results	Comments
Becker et al., 1968, U.S.A. (*8*).	Rat.	Controlled populations of pregnant rats were injected twice daily with doses of nicotine varying from .5 mg./kg. to 5 mg./kg. Effects on pregnant rats and newborn were studied.	(*a*) With the lower dosage of nicotine, the birthweights, survival, and developmental status did not differ from controls. (*b*) With thhe higher dosage, pregnant rats consumed less food and gained less weight than control mothers. Delivery dates were prolonged 2 to 4 days or more. Young were underweight and fetal in appearance. There were no abortions and no premature young.	Control rats were injected with saline.
Tjälve et al., 1968, Sweden (*48*).	Mouse.	The passage of ^{14}C-nicotine and its metabolites from the mother into the fetuses was studied.	(*a*) Nicotine and its metabolites accumulated in the placenta and passed into the fetus. (*b*) The metabolites present in the fetus originated from the mother. (*c*) The passage of nicotine into the fetus was the same during the last four days of pregnancy.	
Fabro and Sieber, 1969, U.S.A. (*11*).	Rabbit.	(1-methyl-^{14}C)-caffeine and G-(^{3}H)-nicotine were given to 6-day pregnant rabbits. The dose for nicotine was 50 μg./kg., intravenous, producing plasma levels similar to those attained in man by cigarette smoking (.06–.09 μg./ml.).	(*a*) One hour after (^{3}H)-nicotine treatment, a high level of radioactivity compared with that in maternal plasma was found in uterine secretion (ratio = 10.8). (*b*) Unchanged radioactive nicotine and some of its metabolites were present in the preimplantation blastocyst (blastocyst/plasma ratio $\simeq$ 3).	Radioactivity in uterine secretion was not found in nonpregnant controls.

TABLE 6.—*Animal experimental data on the effect of smoking and nicotine on pregnancy (cont.)*

Author, year, country, reference	Animal	Design of study	Results	Comments
Welch et al., 1969, U.S.A. (*52*).	Rat.	Rats which were pregnant for 18 days were given 40 mg./kg. of 3,4-benzpyrene; 1,2-benzanthracene; 1,2,5,6-dibenzanthracene; chrysene; 3,4-benzofluorene; anthracene; pyrene; fluoranthene; perylene; or phenanthrene orally, and BP-hydroxylase activity in the placenta was measured 24 hours later.	All compounds tested stimulated: BP-hydroxylase activity in the placenta. 1,2-benzanthracene was the most active inducer of BP-hydroxylase.	Placenta from control rats possessed very low BP-hydroxylase activity.
Younoszai et al., 1969, Canada (*57*).	Rat.	Pregnant rats were exposed to smoke from regular tobacco cigarettes, non-nicotine cigarettes made with lettuce leaves, and non-nicotine cigarettes (lettuce leaves) to which 15 mg. of nicotine was added. The rats were forced to inhale cigarette smoke by placing their cages in a smoking chamber. CO levels were maintained between 2 and 8 percent by exposing the animals to smoke 5 times a day at 2-hour intervals. Other groups of rats were fed restricted diets, receiving from 55 to 80 percent of the food consumed by control rats.	(*a*) Fetuses of all smoked rats were growth retarded compared to control animals, those exposed to tobacco smoke (cigarette) being most severely affected. (*b*) The amount of food consumed by rats exposed to cigarette smoke was reduced. (*c*) There was a significant direct relation between fetal body weight and the average amount of food eaten during pregnancy. (*d*) Fetal weight was reduced in prpportion to the decrease in maternal food intake in the two groups of rats exposed to the lettuce leaf cigarette smoke. In rats exposed to tobacco cigarettes, fetal weight was reduced more than expected from the decrease in maternal food intake.	Control rats were handled in the same way except that they were not exposed to cigarette smoke.
Canada (*51*). Kirschbaum et al., 1970, U.S.A. (*18*).	Sheep.	Intravenous injection of fresh solutions of nicotine, and simulated smoking of cigarettes. were carried out upon pregnant ewes. Cardiovascular functions, including gaseous exchange and blood flow of both the ewes and their fetuses were studied for acute effects.	No significant changes were observed as a result of either nicotine administration or smoke inhalation.	Each experiment included a control period during which attainment of a steady state was the aim.

isotope studies in mice (*48*) have indicated that nicotine and its metabolites accumulate in the placenta and are passed into the fetus.

Many of the experimental studies were designed to determine the pathophysiology of the effect of maternal smoking on the fetus. The experimental conditions in the several studies varied greatly as did the results. No unified concept of the effect of maternal smoking on fetal growth or on the outcome of pregnancy can be derived from the presently available research.

SUMMARY

Maternal smoking during pregnancy exerts a retarding influence on fetal growth as manifested by decreased infant birthweight and an increased incidence of prematurity, defined by weight alone. There is strong evidence to support the view that smoking mothers have a significantly greater number of unsuccessful pregnancies due to stillbirth and neonatal death as compared to nonsmoking mothers. There is insufficient evidence to support a comparable statement for abortions. The recently published Second Report of the 1958 British Perinatal Mortality Survey, a carefully designed and controlled prospective study involving large numbers of patients, adds further support to these conclusions.

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CHAPTER 6

Peptic Ulcer

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Peptic Ulcer

It has been estimated that 10 to 12 percent of all people will suffer from peptic ulcer disease at some time in their lives (*17*). In the U.S.A. in 1967, there were 5,323 deaths from gastric ulcer and 4,502 deaths from duodenal ulcer (*22*). Several studies have documented an association between smoking and peptic ulcer disease, which is stronger for gastric ulcer than for duodenal ulcer.

Prospective studies indicate that male cigarette smokers have increased peptic ulcer mortality ratios (see table 1). Although a trend toward increased mortality from gastric ulcer is seen in cigar and/or pipe smokers, the data do not allow significant conclusions to be drawn. Similarly, no firm conclusions can be drawn about female smokers.

Retrospective studies have consistently shown smaller numbers of nonsmokers in the peptic ulcer groups than in matched control populations (tables 2 and 3).

Cigarette smoking has been shown to reduce the efficacy of antacid therapy in documented peptic disease (*3*) and to slow peptic ulcer healing (*7*). One study indicated that smokers who had undergone surgical treatment for their peptic disease had more major complications, including recurrence of peptic disease, than nonsmokers (*14*).

Numerous studies in both animals and man have been performed to investigate the effect of smoking or the administration of nicotine on the gastrointestinal tract. Studies of gastric secretion and motility in normal controls and in patients with peptic ulcer disease as well as in experimental animals have produced conflicting results (*4, 16, 18, 19, 20*).

SUMMARY

Cigarette smoking males have an increased prevalence of peptic ulcer disease and a greater peptic ulcer mortality ratio. These relationships are stronger for gastric ulcer than for duodenal ulcer. Smoking appears to reduce the effectiveness of standard peptic ulcer treatment and to slow the rate of ulcer healing.

TABLE 1.—*Smoking and peptic ulcer disease mortality*

(Numbers in parentheses represent actual number of deaths)

SM = Smokers NS = Nonsmokers G = Gastric D = Duodenal

Author, year, country, reference	Number and type of population	Data collection	Actual deaths SM	Actual deaths NS	Mortality ratios	Comments
Doll and Hill, 1964, Great Britain (*5, 6*).	41,000 male British physicians.	Questionnaire and follow-up of death certificate.	54		Cigarettes/day: †Peptic — NS 1.00; All cigarette 7.00; 1–14 gs. per day 2.33; 15–24 10.33; >25 7.33. Pipe/cigar: Gastric 4.00	† Total number of deaths were too small to allow separate examinations.
Hammond, 1966, U.S.A. (*11*).	440,558 males 35–84 years of age in 25 States.	Interviews by ACS volunteers	G–83	11	NS ..... 1.00 (11) 1.00 (22); SM (age 45–64) 2.95 (83) 2.86 (93); SM (age 65–79) 4.06 (83) 1.50 (93)	
Kahn, 1966, U.S.A. (*12*).	U.S. male veterans 2,265,674 person years.	Questionnaire and follow-up of death certificate.	G–78 .....12 D–119 25		NS ..... 1.00(12) 1.00(25); SM; All cigarette .... 4.13(39) 2.98(57); 1–9 ..... 3.95 (5) 2.30 (6); 10–20 ..... 2.77(13) 2.74(26); 21–39 ..... 5.45(15) 3.98(22); >39 .....11.57 (6) 2.89 (3). Pipe: 1.00(12) 1.00(25); 2.84 (4) 1.59 (5). Cigar: 1.00(12) 1.00(25); 2.90 (7) 1.58 (8).	
Weir and Dunn, 1970, U.S.A. (*23*).	68,153 males in various occupations in California.	Questionnaire and follow-up of death certificate.	44		NS ..... 1.00; All cigarette .... 0.53; ±10 ..... 1.00 0.40; ±20 ..... 1.67 0.59; ≧30 ..... 2.38 0.32	No deaths from gastric ulcer occurred in nonsmokers and risk of those smoking ±10/day was set at 1.00. NS included pipe, cigar, and ex-smokers.

TABLE 2.—*Methods used in retrospective and cross sectional studies of peptic ulcer and smoking*

Author, year, country, reference	Sex	Cases		Controls		Comments
		Number	Method of selection	Number	Method of selection	
Barnett, 1927, U.S.A. (*2*).	M	66 Gastric. 178 Duodenal	Patients admitted between 1913 and 1926. Only cases with complete smoking history selected.	500	Selected at random from the general admissions-males, 20–60 years of age.	1. Retrospective review records at Peter Bent Brigham Hospital. 2. Ulcer diagnosis probably well established.
Trowell, 1934, England (*21*).	M	50 Duodenal	Not stated	400	Selected at random from wards of a general hospital.	1. Interviewed by investigator. 2. Ulcer diagnosis confirmed by X-ray and/or surgery.
Allibone and Flint, 1958, England (*1*).	M and F	107	Consecutive admissions to hospital of patients with gastric and duodenal hemorrhage or perforation.	107	Matched by age, sex, and time of admission from acute general surgical emergency admissions.	Patients and controls interviewed by same observer.
Doll et al., 1958, England (*7*).	M and F	327 Gastric. 338 Duodenal.	Ulcer patients in Doll and Hill Lung Cancer Study plus additional patients in Central Middlesex Hospital.	1,143	Patients with non-ulcer diseases. Each case matched with 2 control patients of same sex, 5-year age group, and same type of place of residence. Male patients matched by social class.	1. Same interviewers and questionnaire in cases and controls. 2. Ulcer diagnosis probably well established.
Edwards et al., 1959, England (*8*).	M	1,737	Men aged 60 and over on 11 General Practioners' lists were examined and interviewed by these practitioners. Represents about 84 percent of all such men on these lists. (9 percent non-response due to death and/or untraced.)			Of 143 considered to have a peptic ulcer, 53 were confirmed by X-ray.